

Combination Products: Industry Strategies and Innovation Takes Combination Products to New Levels

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Fred Miller, CEO of INNERCAP Technologies in Tampa, Florida, has been in the consumer products industry for twelve years. He has been involved with developing, manufacturing, branding and marketing of consumer products. While working on a combination consumer product with incompatible compounds, he developed the patent-pending, multi-phase, multi-compartment delivery technology to overcome this common, but difficult to resolve, formulation issue. Currently, the company is actively out-licensing the technology for combination products to companies operating in this growing space.

Introduction

Combination pharmaceutical products, while not a new concept, is a product strategy whose time has come. In most industries, opportunities previously by-passed or shelved can be turned into viable products with enormous market potential when combined with other technological advances. A prime example of this is the digital camera, originally developed by Kodak. Digital camera technology was shelved for twenty years because it required advances in computer processors and other technologies and because it was viewed as a threat to the existing and less expensive film technology. Since its launch, the market and applications for digital photography have expanded rapidly and exceeded all expectations. Technological advances in all industries drive innovation to levels that were never imagined or thought practical in the past.

Capsule Technology

The pharmaceutical industry reveals similar instances of by-passed technologies: the re-emergence of liquid-filled, two-piece, hard-shell capsule technology is a prime example. Companies, such as **Shionogi** and **Capsugel**, have identified this capsule as a viable opportunity for both pharmaceutical and biopharmaceutical companies for developing new products (*Figure 1*). For a number of



Figure 1 – A liquid-filled capsule; an example of technology from Shionogi and Capsugel.

Liquid-filled, two-piece, hard-shell capsule benefits

- Faster development
- Increases bioavailability of insoluble compounds
- Requires less excipients
- Requires less API to work with during development
- Benefits highly potent low-dose applications
- Good content uniformity
- Several different capsule shell materials available to work with
- Dosage form typically increases compliance

Table 1 – The benefits of liquid-filled, two-piece, hard shell capsules.

reasons, the timing today makes sense whereas in the past, due to industry practices, it received little attention. NCE development has become more expensive and development cycles have become much longer. Although the technology originated approximately ninety years ago, it now looks very promising in a number of different applications, such as the delivery of insoluble compounds and biopharmaceuticals (*Table 1*). Furthermore, the pharmaceutical industry is using life cycle management strategies to meet investor demands.

With approximately 40% of the currently marketed products having poor solubility, and an enormous number of potential candidates in pharma databanks shelved due to poor solubility, new delivery strategies are of great interest to the industry. One of the most promising strategies to deliver these insoluble compounds is using dissolved systems. Using lipids, liquids or semi-solids to formulate new products has many benefits at different levels. Some of these benefits include fewer excipients in the formulation, faster development, less API required, greater bioavailability, content uniformity, faster absorption and increased compliance. Two-piece hard-shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations. As the new insoluble compounds are commercialised in liquid-filled capsules, they will become available for new combination products.

Combination Products

Combination pharmaceutical products are defined as being able to treat the same disease state, multiple disease states, or counteract the negative side-effects.

- 'Additivity' is combining two or more drugs with complementary modes of action to gain the desired therapeutic effect without the side-effects;
- 'Potentiation' is the synergistic effect on drug A by adding a dose of drug B without a therapeutic effect;
- 'Cancellation' is when effects of one drug are nullified by the addition of a second.

A combination product may contain pharmaceuticals, biopharmaceuticals, or nutraceuticals. They can also incorporate several, different controlled-release profiles, such as immediate, pulse, chronotherapy, targeted and sustained. The pharmaceutical industry is placing a greater emphasis on combination products and commercialising poorly-soluble compounds due to their limited pipelines of soluble compounds.

With the successful evolution of combination products, companies will continue to place increasing resources on developing new, innovative and beneficial combination products. Layered tablets have provided a successful approach in delivering combination products, primarily consisting of compatible, soluble compounds. Some of these layered tablets have included different release profiles for each compound in order to achieve the most beneficial release profile for each active (Table 2).

The National Pharmaceutical Council estimates that non-compliance accounts for up to \$100 billion in additional healthcare and productivity costs. Furthermore, a concerted effort to increase patient compliance can result in significant savings worldwide. With this in mind, there will continue to be a demand for ways to increase compliance; combination products are one of the most successful strategies. Combination products, containing two or more compounds with complementary actions, represent an innovation that has increased the possible therapeutic options in the treatment of almost every disease. Acceptance of such products is increasingly apparent among physicians, patients, insurers and the FDA.

Fixed-dose combination benefits

- Increasing patient compliance with therapy
- Increasing efficacy by optimising timing of medicaments
- Minimisation of side-effects and adverse effects
- Enhancement of pharmacokinetic characteristics of each compound
- Increased patient quality of life
- Optimisation of institutional resources by minimising administrations
- Minimising patient length of stay in institutional facilities
- Revitalises a brand
- Life cycle management strategy
- Reduces impact of generic competition
- Less financial risk than developing a new compound
- One insurance co-pay

Table 2 – Fixed-dose combination benefits.

Company	Brand name	Therapeutic area	Combination
Eli Lilly and Company	Symbax	Bipolar depression	Prozac & Zyprexa
Gilead Sciences	Truvada	Anti-HIV	Viread & Emtrivia
GlaxoSmithKline	Advair	Asthma	Flovent & Serevent
GlaxoSmithKline	Epzicom	Anti-HIV	Epivir & Ziagen
Merck/Schering-Plough	Vytorin	High cholesterol	Zocor & Zetia
Novartis	Lotrel	Hypertension	Lotensin & Norvasc
Pfizer	Caduet	Cardiovascular disease	Lipitor & Norvasc

Table 3 – Recently launched combinations.

Combination Drug Products

There are currently at least twelve combination drug products in the top selling pharmaceutical products. Several new ethical combination products have been approved by the FDA recently, such as **Pfizer's** Caduet, **Merck/Schering-Plough's** Vytorin and **Gilead Sciences'** Truvada. Pfizer's Caduet was unique in being the first product that combined two drugs to treat two different, but concomitant disease states. In the consumer sector, there are over 200 combination products that are the best selling products in areas such as cough/cold and analgesics (Table 3).

As companies continue to identify, develop and commercialise the most beneficial combinations using soluble compounds, there will be a limited number of these soluble combinations available to work with. When this transition begins gaining momentum, companies will start to place a greater emphasis on incorporating insoluble compounds with soluble compounds into these combination products.

A Multi-phase, Multi-compartment Capsule-based Delivery System

There are numerous strategies that can be applied when developing combination products with soluble compounds. However, new strategies will have to be used when considering combinations with soluble and insoluble compounds.

Different physical phases will have to be used to achieve the greatest pharmacokinetic profile for a number of these compounds. This will result in the need for multi-phase delivery systems to deliver them. **INNERCAP Technologies** has developed a proprietary multi-phase, multi-compartment capsule-based delivery system that can deliver incompatible and compatible drugs using different physical phases (Figures 2 and 3). Each compartment is sealed to prevent the medicaments from escaping and coming into contact with one another. If a compound is currently stable within a capsule, stability problems are precluded in a multi-capsule application (Table 4).

As with any new combination drug project, a combination drug may not work in a specific dosage form due to incompatibility or other formulation issues and an



Figure 2 – An example of a multi-phase, multi-compartment dosage form. Four individual compounds are combined into one single dosage form. The combination consists of a high-potency, insoluble active in a lipid emulsion, sustained-release tablet and cocktail of two crystalline active materials. A combination of release profiles can be incorporated in the system.

alternative delivery system will have to be identified. For instance, both bi-layer tablets and multi-compartment capsules have specific benefits associated with the dosage form. If the combination product will contain incompatible or multi-phase compounds, multi-compartment capsules can make a project possible that may otherwise fail in a bi-layer tablet. This new development may make viable projects that may have failed in the past and it dramatically increases the possibilities when working with different combinations.

Furthermore, multi-compartment capsules can accelerate the development of a combination product and facilitate to clinical trials by bypassing the formulation development of a combination tablet project. This allows a combination product to enter clinical trials and expedites the process to determine if the new product achieves the desired therapeutic effects in the trial group. This approach can save millions of dollars in development costs, and a first-to-market advantage can mean the success or failure of a multi-million dollar product in the marketplace.

Typically, the technology is not restrained by the use of a specific capsule material. The outer walls of the compartments are formed of an acceptable soluble ingredient, such as gelatin, starch, hydrophilic polymers or hydroxypropyl methyl-cellulose (HPMC). These



Figure 3 – INNERCAP blue-banded capsule.

INNERCAP™, multi-phase capsule benefits

- Allows incompatible compounds to be delivered in a single dosage form
- Allows different release profile for each compound
- Reduces development time to start clinical trials
- Allows multi-phase excipients for greatest pharmacokinetic profile
- Requires less API to work with during development
- Capsules do not damage heat sensitive API
- Increases compliance
- Provides unique marketing and branding opportunities
- Reduces counterfeiting
- Increases speed to market

Table 4 – INNERCAP™, multi-phase capsule benefits.

provide a barrier for containing the active ingredient or medicament within the internal periphery of the walls. The most appropriate chamber material is determined by the medicaments that will come into contact with the shell material; a single capsule could use combinations of acceptable shell materials. The release profiles can be incorporated into the shell materials, or coatings can be applied to target or control the release of the medicaments from the compartments. Also, release profiles can be applied to the active compounds filled into each capsule in a number of ways. One example would be the use of enteric-coated pellets with different release profiles to bypass the stomach.

Marketing departments seek new drug delivery systems as well, especially if it gives them an opportunity for a unique marketing campaign. For example, **Wyeth's** liquid filled Advil capsules and **McNeil's** recently introduced Tylenol Rapid Release Gel Capsules have been very successful products because consumers perceive from visual images and marketing benefits how they can benefit from using these new products.

Conclusion

New drug delivery technologies will continue to be developed and will make exciting products possible that were never previously imagined. These new drug delivery technologies will, no doubt, create countless innovative products and, as with digital photography, lead to unimagined, new frontiers.

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